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Original Article

ALBUMIN, LEUKOSIT, AND PROTROMBIN AS PREDICTORS OF SEPSIS MORTALITY AMONG ADULT PATIENTS IN SOETOMO GENERAL HOSPITAL, SURABAYA, INDONESIA**Rahmat Sayyid Zharfan^{1a}, Ahmad Lukman Hakim², Abdul Khairul Rizki Purba^{2,3}, Soni Sunarso Sulistiawan⁴, Bambang Pujo Semedi⁴**¹Faculty of Medicine, Universitas Airlangga, Surabaya²Department of Pharmacology, Faculty of Medicine, Universitas Airlangga, Surabaya³Department of Health Sciences, University Medical Centre Groningen, University of Groningen, The Netherlands⁴Department of Anesthesiology and Reanimation, Faculty of Medicine, Universitas Airlangga/Dr Soetomo Academic Hospital, Surabaya^a Corresponding author: zharfan.rs@gmail.com**ABSTRACT**

Introduction: Sepsis is presented as a complex and multifactorial syndrome where the morbidity and mortality rates still high around the world. Strong evidence with regard to early predictive factors for mortality and morbidity is rare to be provided. **Objective:** The aim of this study was to analyse the prominent predictors from the values of laboratory findings among patients with sepsis. **Method and Material:** The study was an analytic observational study with a case-control approach. The data were extracted from patients' medical records between 2014 and 2015. This study involved 50 septic patients admitted to Dr. Soetomo General Hospital, Surabaya, Indonesia. Blood urea nitrogen (BUN), creatinine serum, albumin, leukocytes count, haemoglobin, hematocrite, platelets, sodium, potassium, chloride, prothrombin time (PT), and activated partial thromboplastin time (APTT) were collected from blood samples. Logistic regression was used to estimate sepsis related mortalities frequencies and the relationship between laboratory findings and under 28-days mortality. **Result and Discussion:** From 50 patients, 22 patients were died (44%). The regression model was initially conducted using all three biomarkers as covariates, then using backward elimination, the covariate with the highest p-value was eliminated. The process was repeated until covariates with statistically significant remained. Multivariate analysis showed that albumin, leukocytes count, and prothrombin time (PT) were the findings associated with high mortality. The independent predictors of mortality identified by further multivariate regression analysis were taken into account as a lower than 3.5 g/dL of albumin, above 12.000/ μ L of leukocytes count, and prolonged more than 14 seconds of prothrombin time; with p value <0,05 respectively (0.029; 0.049; 0.027). **Conclusion:** Notably, low albumin level, elevated levels of leukocytes, and prolonged prothrombin time were clinically considered as independent predictors of mortality among adult patients with sepsis.

Keywords: Albumin, Leukocyte, Mortality, Prothrombin Time, Sepsis.**ABSTRAK**

Pendahuluan: Sepsis digambarkan sebagai sindrom yang kompleks dan multifaktorial dimana angka morbiditas dan mortalitas tetap tinggi di seluruh dunia. Bukti yang kuat sehubungan dengan faktor prediktif awal untuk mortalitas dan morbiditas jarang tersedia. **Tujuan:** Tujuan dari penelitian ini adalah untuk menganalisis prediktor yang menonjol dari nilai-nilai temuan laboratorium di antara pasien dengan sepsis. **Metode dan Bahan:** Penelitian ini merupakan studi observasional analitik dengan pendekatan case-control. Data diambil dari rekam medis pasien antara tahun 2014 dan 2015. Penelitian ini melibatkan 50 pasien sepsis yang dirawat di Rumah Sakit Umum Daerah Dr Soetomo, Surabaya, Indonesia. Blood Urea Nitrogen (BUN), serum kreatinin, albumin, jumlah leukosit, hemoglobin, hematokrit, platelet, natrium, kalium, klorida, prothrombin time (PT), dan activated partial tromboplastin time (APTT) dikumpulkan dari sampel darah. Regresi logistik digunakan untuk memperkirakan tingkat kematian sepsis dan hubungan antara temuan laboratorium dan mortalitas 30 hari. **Hasil dan Pembahasan:** Dari 50 pasien, 22 didapatkan meninggal (44%). Model regresi pertama kali disusun menggunakan biomarker sebagai kovariat. Dengan menggunakan metode eliminasi mundur, kovariat dengan nilai-p tertinggi dihilangkan dan modelnya diarahkan ke tiga biomarker yang tersisa. Proses ini diulang

sampai terdapat hanya biomarker yang secara statistik signifikan dipertahankan dalam model. Analisis multivariat menunjukkan bahwa albumin, jumlah leukosit, dan prothrombin time (PT) adalah temuan yang terkait dengan mortalitas yang tinggi. Prediktor independen mortalitas diidentifikasi oleh analisis regresi multivariat, lebih lanjut dinyatakan: albumin yang lebih rendah dari 3,5 g/dL, jumlah leukosit di atas 12.000/ μ L, dan prothrombin time memanjang lebih dari 14 detik; dengan nilai $p < 0,05$; berturut-turut (0,029; 0,049; 0,027). **Kesimpulan:** Khususnya, kadar albumin yang rendah, peningkatan kadar leukosit, dan prothrombin time yang memanjang secara klinis dianggap sebagai prediktor independen mortalitas di antara pasien dewasa dengan sepsis.

Kata kunci: Albumin, Leukosit, Kematian, Waktu Prothrombin, Sepsis

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INTRODUCTION

Sepsis is presented as a complex and multifactorial disease where the morbidity and mortality rates remain high around the world.¹ Sepsis is still an extraordinary challenge in the intensive care unit because of the high mortality rate regardless of providing optimal care. The use of serum biomarkers has significantly increased the ability of doctors to diagnose and predict the prognosis of sepsis.¹

In clinical practice, the number of leukocytes has been most widely used as a biomarker that is sufficient to guide the assessment of clinical progress among septic patients, even in addition to other laboratory parameters such as lactate acid, procalcitonin and c-reactive protein. Nevertheless, such parameters obviously remain unavailable particularly in the remote area and led to noteworthy impact on the hospital cost. In Indonesia, a previous study reported that the proportion of patients with sepsis was accounted for 27.08% severe sepsis, 14.58% septic shock, while 58.33% remaining on the state of sepsis, which the mortality rate ranged of 40-60% in severe sepsis.²

Complex pathophysiology of sepsis, which need more than one biomarker to be able to describe host responses to this diseases. Combination of several biomarkers into certain classification rule will improve the

accuracy and applicability. The purpose of this study was to obtain predictive value using combination of several biomarker, such as: leukocyte count, albumin, and coagulation factors, which associated with under 28-days mortality in septic patients. Strong evidence with regard to early predictive factors for mortality and morbidity is scarcely provided. The aim of this study is to analyse the prominent predictors from the values of laboratory findings among patients with sepsis.

MATERIAL AND METHOD

The study was a analytic observational study with a case-control approach. The data was extracted from patient's medical records between 2014 and 2015. This study involved 50 septic patients admitted to Soetomo General Hospital, Surabaya, Indonesia.

Adult patients who fulfilled the criteria for sepsis were collected. Adult patient who have received antibiotics for more than 24 hours before the blood sample taken was excluded. Baseline and demographic data were collected, such as: sex, age, admission category, main site of infection, and comorbidity.

Blood urea nitrogen (BUN), creatinine serum, albumin, leukocytes count, haemoglobin, hematocrite, platelets, sodium, potassium, chloride, activated partial thromboplastin time (APTT), and prothrombin time (PT) were collected from

blood samples. A multivariate logistic regression was conducted to estimate correlation between covariates of laboratory findings and under 28-days sepsis related mortality.

RESULT AND DISCUSSION

The author used multivariate logistic regression to model biomarker capabilities to identify patients who had outcome of

mortality under 28 days. The regression model was initially constructed using whole biomarkers provided as covariates. The covariate with the highest *p*-value was removed using backward elimination method, and the model was continued to the remaining three biomarkers. This process is repeated until the author got the biomarkers which are statistically significant remain in the model.

Table 1. Leukocyte Count, Prothrombin Time (PT), And Albumin Predictive Performance For Mortality In Sepsis Patient

Biomarker	All N=50	Survivor n=28	Non Survivor n=22	<i>P</i>	AUROC	Cut-off
Leukocytes	13370	12463.57	14523.63	0.049	0.606	12800
Albumin	2.92	3.21	2.55	0.029	0.750	2.217
PT	19.81	18.19	21.86	0.027	0.649	14.2

Note. Description of the two groups was done using the Compare Means test. AUROC = area under the receiver operating characteristic curve, PT = prothrombin time

According to result of regression equation, the author converted the probability of under 28-days sepsis related mortality, which represents final predictor of sepsis related mortality.

In Table 1, from 50 patients, 22 patients were died (44%). Multivariate analysis showed that albumin, leukocytes count, and prothrombin time (PT) were associated with high mortality. The independent predictors of mortality identified by further multivariate regression analysis were taken into account as a lower level of 3.5 g/dL albumin, *p* value 0.029; above 12.000/ μ L of leukocytes count, *p* values 0,049; and prolonged 14 seconds of prothrombin time, *p* value 0.027.

The AUROC (Area Under The Receiver Operating Characteristic Curve) model from sepsis related mortality and each of the constituent biomarkers for the prediction of under 28 days mortality is shown in Figure 1. The author found that the AUROC is from the

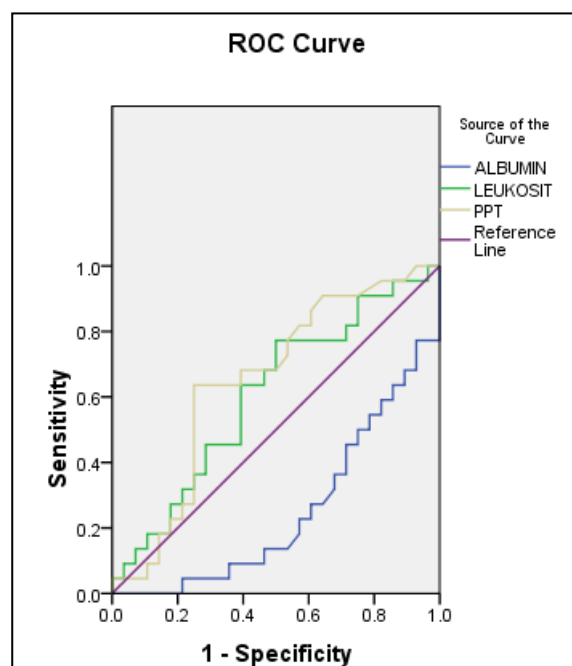


Figure 1. Receiver Operating Characteristic (ROC) Curve of leukocyte count, prothrombin time, and albumin level

model: leukocyte, prothrombin time (PT), and albumin was 0.606; 0.649; and 0.750 (95%

CI), which suggested fairly good model discrimination. The sepsis mortality scores outperform biomarkers of individual constituents in predicting mortality under 28 days; These biomarkers show moderate performance to good performance when used.

In this observational analytic study, the author collected the historical data of 50 patients with sepsis and studied three biomarkers on their hospital admissions which were used in the prediction of those patients who had the risk of under 28-days mortality. Sepsis-related mortality predictors using baseline leukocytes count, prothrombin time (PT) and albumin level could reflect the outcome of under 28-days mortality with a fairly good performance.

Biomarkers, especially a combination of the two components, can provide more reliable guidance for predicting the outcome; mortality in sepsis. Recent studies,^{3,4} also stated that combination biomarkers performed better than other clinical scores used routinely in predicting sepsis-related mortality.

Sepsis itself, often ensures disrupted coagulation function, ranging from mild changes to severe disseminated intravascular coagulation (DIC). Septic patients with severe DIC may experience the thromboembolic disease sign, as fulminant purpura or clinically obscure microvascular fibrin deposition, which strongly indicates multiple organ dysfunction. On the other hand, severe bleeding may be the main symptom, or even bleeding and thrombosis.⁵ The disrupted coagulation mechanism, specifically DIC, is an important predictor and one of possible clinical outcomes in patients with severe sepsis.⁶

Initiation of coagulation activated by proinflammatory cytokines such as IL-6, depends on tissue factors (TF). Increased thrombin formation is caused by tumor necrosis factor (TNF- α) which breaks down

the damaged physiological anticoagulant mechanism while the spread of fibrin deposition in microvasculature is caused by inadequate fibrin degradation, as a result of the inhibited fibrinolytic system.⁶ The complex TF-factor-VIIa catalyzes the activation of both factors IX and factors X, increasing the activation of factor X and prothrombin, respectively.⁸

Our results are related to the combined use of leukocyte counts, prothrombin time (PT) and albumin level activity for sepsis-related mortality prediction. Even though the results are encouraging, this study still has limitations. The prediction of sepsis deaths that we produce is that single data is predicted, but whether it can be generalized to an external population was unknown. Clinical outcomes depend on the patient management, which can vary between each health center; thus, lack of standardization may have disrupted our results. However, the 44% mortality rate found in the population is almost representing to that condition observed in Indonesia.² Even though the author tried to control confounders by other clinical variables by modeling sepsis death scores in the logistic regression model. The author might find some impediments to explain the other unmeasured confounders factors. Besides these findings, since this study using convenience sample, selection bias might lead to less representative population. Thus, further research is needed to improve and validate the clinical applicability of this sepsis-related mortality predictor in reflecting the clinical outcome in sepsis treatment.

CONCLUSION

Notably, low albumin level, elevated levels of leukocytes, and prolonged prothrombin time were clinically considered as independent predictors of mortality among

adult patients with sepsis. Further research is needed to develop these findings and to assess whether these sepsis mortality predictor derived from biomarkers, into certain classification and score, then can be successfully integrated with physicians' clinical practice to improve reflection, prediction and clinical decision making at the patient's clinical setting.

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Conflict of Interest

There is no conflict of interest to be declared

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